CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074857

Trade Name : TRIAMTERENE AND HYDROCHLORTHIAZIDE CAPSULES 37.5MG/25MG

Generic Name: Triamterene and Hydrochlorthiazide Capsules 37.5mg/25mg

Sponsor : Geneva Pharmaceuticals, Inc.

Approval Date: September 9, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074857

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074857

APPROVAL LETTER

ANDA 74-857

SEP 9 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
Agent for: Novartis Pharmaceuticals
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application dated February 12, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg.

Reference is also made to your amendments dated November 27, 1996; and March 28, April 8, and May 8, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Dyazide® Capsules 37.5 mg/25 mg of SmithKline Beecham Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

9/9/97

Douglas L. Spotn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074857

FINAL PRINTED LABELING

Triamterene and Hydrochlorothiazide Capsules, USP

37.5 mg/25 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

Geneva pharmaceuticals, inc.

N 3 0781-2056-10 3

Each capsule contains: Triamterene, USP 37.5 mg
Hydrochlorothiazide, USP 25 mg

Usual Dosage: 1 or 2 capsules once daily. See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light.
Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
ISS 95-11M

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

N96/8

SEP 9 1997

APPROVED

LOT:

EXP.:

Triamterene and Hydrochlorothiazide Capsules, USP

37.5 mg/25 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

Geneva pharmaceuticals, inc.

N 3 0781-2056-01 1

Each capsule contains: Triamterene, USP 37.5 mg
Hydrochlorothiazide, USP 25 mg

Usual Dosage: 1 or 2 capsules once daily. See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from light. Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
ISS 95-11M

Manufactured By
Geneva Pharmaceuticals, Inc
Broomfield, CO 80020

N96/8

SEP 9 1997

APPROVED

LOT:

EXP.:

7188

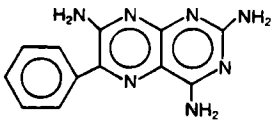
TRIAMTERENE AND HYDROCHLOROTHIAZIDE CAPSULES, USP

7188-4

DESCRIPTION: Triamterene is an antikaliuretic agent and hydrochlorothiazide is a diuretic/antihypertensive agent.

At 50°C, triamterene is practically insoluble in water (less than 0.1%). It is soluble in formic acid, sparingly soluble in methoxyethanol, and very slightly soluble in alcohol.

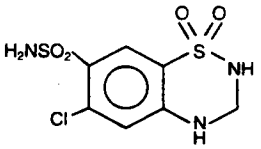
Triamterene is 2,4,7-triamino-6-phenylpteridine with a chemical formula of $C_{12}H_{11}N_7$ and a molecular weight of 253.27. The structural formula for triamterene is:



TRIAMTERENE

Hydrochlorothiazide is slightly soluble in water. It is soluble in dilute ammonia, dilute aqueous sodium hydroxide, and dimethylformamide. It is sparingly soluble in methanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2, 4-benzothiadiazine-7-sulfonamide 1,1-dioxide with a chemical formula of $C_7H_8ClN_3O_4S_2$ and a molecular weight of 297.75. The structural formula for hydrochlorothiazide is:



HYDROCHLOROTHIAZIDE

Each capsule, for oral administration, contains 37.5 mg triamterene and 25 mg hydrochlorothiazide. Inactive ingredients include: citric acid, glycine, anhydrous lactose, magnesium stearate, Polysorbate 80, povidone, and sodium starch glycolate. The capsule shells and imprinting inks contain: D & C Yellow #10 Aluminum Lake, FD & C Blue #1 Aluminum Lake, FD & C Blue #2 Aluminum Lake, FD & C Red #40 Aluminum Lake, gelatin, pharmaceutical glaze, propylene glycol, synthetic black iron oxide, and titanium dioxide.

This product complies with dissolution test #3.

CLINICAL PHARMACOLOGY: Triamterene and hydrochlorothiazide is a diuretic/antihypertensive drug product that combines natriuretic and antikaluretic effects. Each component complements the action of the other.

The triamterene component of triamterene and hydrochlorothiazide capsule exerts its diuretic effect on the distal renal tubule to inhibit the reabsorption of sodium in exchange for potassium and hydrogen ions. Its natriuretic activity is limited by the amount of sodium reaching its site of action. Although it blocks the increase in this exchange that is stimulated by mineralocorticoids (chiefly aldosterone) it is not a competitive antagonist of aldosterone and its activity can be demonstrated in adrenalectomized rats and patients with Addison's disease. As a result, the dose of triamterene required is not proportionally related to the level of mineralocorticoid activity, but is dictated by the response of the individual patients, and the kaluretic effect of concomitantly administered drugs. By inhibiting the distal tubular exchange mechanism, triamterene maintains or increases the sodium excretion and reduces the excess loss of potassium, hydrogen, and chloride ions induced by hydrochlorothiazide. As with hydrochlorothiazide, triamterene may reduce glomerular filtration and renal plasma flow. Via this mechanism it may reduce uric acid excretion, although it has no tubular effect on uric acid reabsorption or secretion. Triamterene does not affect calcium excretion. No predictable antihypertensive effect has been demonstrated for triamterene.

The hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

Duration of diuretic activity and effective dosage range of the hydrochlorothiazide and triamterene components are similar. Onset of diuresis with triamterene and hydochlorothiazide takes place within one hour, peaks at two to three hours and tapers off during the subsequent seven to nine hours.

Triamterene and hydrochlorothiazide capsule are well absorbed.

It has been reported that upon administration of a single oral dose to fasted normal male volunteers, the following mean pharmacokinetic parameter

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Triamterene and hydrochlorothiazide capsule are well absorbed.

It has been reported that upon administration of a single oral dose to fasted normal male volunteers, the following mean pharmacokinetic parameters were determined:

	AUC(0-48) ng*hrs/mL (± SD)	Cmax ng/mL (± SD)	Median Tmax hrs	Ae mg (± SD)
triamterene	148.7 (87.9)	46.4 (29.4)	1.1	2.7 (1.4
hydroxytriamterene sulfate	1865 (471)	720 (364)	1.3	19.7 (6.1
hydrochlorothiazide	834 (177)	135.1 (35.7)	2.0	14.3 (3.6

where AUC(0-48), Cmax, Tmax and Ae represent area under the plasma concentration versus time plot, maximum plasma concentration, time to reach Cmax and amount excreted in urine over 48 hours.

One triamterene and hydrochlorothiazide capsule is bioequivalent to a single-entity 25 mg hydrochlorothiazide tablet and 37.5 mg triamterene capsule used in the double-blind clinical trial below. (See Clinical Trials.)

In a limited study involving 12 subjects, coadministration of a marketed brand of triamterene and hydrochlorothiazide capsule with a high-fat meal resulted in: (1) an increase in the mean bioavailability of triamterene by about 67% (90% confidence interval = 0.99, 1.90), p-hydroxytriamterene sulfate by about 50% (90% confidence interval = 1.06, 1.77), hydrochlorothiazide by about 17% (90% confidence interval = 0.90, 1.34); (2) increases in the peak concentrations of triamterene and p-hydroxytriamterene; and (3) a delay of up to 2 hours in the absorption of the active constituents.

Clinical Trials: A placebo-controlled, double-blind trial was conducted to evaluate the efficacy of triamterene and hydrochlorothiazide capsules. This trial demonstrated that triamterene and hydrochlorothiazide capsules 37.5 mg/25 mg were effective in controlling blood pressure while reducing the incidence of hydrochlorothiazide-induced hypokalemia. This trial involved 636 patients with mild to moderate hypertension controlled by hydrochlorothiazide 25 mg daily and who had hypokalemia (serum potassium <3.5 mEq/L) secondary to the hydrochlorothiazide. Patients were randomly assigned to 4 weeks' treatment with once-daily regimens of 25 mg hydrochlorothiazide plus placebo, or 25 mg hydrochlorothiazide combined with one of the following doses of triamterene: 25 mg, 37.5 mg, 50 mg or 75 mg.

Blood pressure and serum potassium were monitored at baseline and throughout the trial. All five treatment groups had similar mean blood pressure and serum potassium concentrations at baseline (mean systolic blood pressure range: 137±14 mmHg to 140±16 mmHg; mean diastolic blood pressure range: 86±9 mmHg to 88±8 mmHg; mean serum potassium range: 2.3 to 3.4 mEq/L with the majority of patients having values between 3.1 and 3.4 mEq/L).

While all triamterene regimens reversed hypokalemia, at week 4 the 37.5 mg regimen proved optimal compared with the other tested regimens. On this regimen, 81% of the patients had a significant ($p<0.05$) reversal of hypokalemia vs. 59% of patients on the placebo/hydrochlorothiazide regimen. The mean serum potassium concentration on 37.5 mg triamterene went from 3.2±0.2 mEq/L at baseline to 3.7±0.3 mEq/L at week 4, a significantly greater ($p<0.05$) improvement than that achieved with placebo/hydrochlorothiazide (i.e., 3.2±0.2 mEq/L at baseline and 3.5±0.4 mEq/L at week 4). Also, 51% of patients in the 37.5 mg triamterene group had an increase in serum potassium of ≥0.5 mEq/L at week 4 vs. 33% in the placebo group. The 37.5 mg triamterene/25 mg hydrochlorothiazide regimen also maintained control of blood pressure; mean supine systolic blood pressure at week 4 was 138±21 mmHg while mean supine diastolic blood pressure was 87±13 mmHg.

INDICATIONS AND USAGE: This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide capsules are indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone.

Triamterene and hydrochlorothiazide capsules are also indicated for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide may be used alone or as an adjunct to other antihypertensive drugs, such as beta-blockers. Since triamterene and hydrochlorothiazide may enhance the action of these agents, dosage adjustments may be necessary.

Usage In Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy. Dependent edema in pregnancy, resulting from restriction of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS:

Antihypertensive Therapy and Potassium Supplementation: Triamterene and hydrochlorothiazide should not be given to patients receiving other potassium-sparing agents such as spironolactone, amiloride or other formulations containing triamterene. Concomitant potassium-containing salt substitutes should also not be used.

Potassium supplementation should not be used with triamterene and hydrochlorothiazide except in severe cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

Impaired Renal Function: Triamterene and hydrochlorothiazide is contraindicated in patients with anuria, acute and chronic renal insufficiency or significant renal impairment.

Hypersensitivity: Hypersensitivity to either drug in the preparation or to other sulfonamide-derived drugs is a contraindication.

Hyperkalemia: Triamterene and hydrochlorothiazide should not be used in patients with preexisting elevated serum potassium.

WARNINGS: Hyperkalemia

Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-sparing diuretic combinations, including triamterene and hydrochlorothiazide. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving triamterene and hydrochlorothiazide when dosages are changed or with any illness that may [illegible]

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If hyperkalemia is suspected (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because hyperkalemia may not be associated with ECG changes.

If hyperkalemia is present, triamterene and hydrochlorothiazide should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium exceeds 6.5 mEq/liter, more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride injection, sodium bicarbonate injection and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see CONTRAINDICATIONS section). Patients with mild renal functional impairment should not receive this drug without frequent and continuing monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide and the pharmacologically active metabolite of triamterene, the sulfate ester of hydroxytriamterene, have been shown to be reduced and the plasma levels increased following triamterene and hydrochlorothiazide administration in elderly patients and patients with impaired renal function.

Hyperkalemia has been reported in diabetic patients with the use of potassium-sparing agents even in the absence of apparent renal impairment. Accordingly, serum electrolytes must be frequently monitored if triamterene and hydrochlorothiazide is used in diabetic patients.

Metabolic or Respiratory Acidosis: Potassium-sparing therapy should also be avoided in severely ill patients in whom respiratory or metabolic acidosis may occur. Acidosis may be associated with rapid elevations in serum potassium levels. If triamterene and hydrochlorothiazide is employed, frequent evaluations of acid/base balance and serum electrolytes are necessary.

PRECAUTIONS:

Impaired Hepatic Function: Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease. Potassium depletion induced by the thiazide may be important in this connection. Administer triamterene and hydrochlorothiazide cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue triamterene and hydrochlorothiazide for a few days. Attention must be given to other factors that may precipitate hepatic coma such as blood in the gastrointestinal tract or preexisting potassium depletion.

Hypokalemia: Hypokalemia is uncommon with triamterene and hydrochlorothiazide but, should it develop, corrective measures should be taken such as potassium supplementation or increased intake of potassium-rich foods. Institute such measures cautiously with frequent determinations of serum potassium levels, especially in patients receiving digitalis or with a history of cardiac arrhythmias. If serious hypokalemia (serum potassium less than 3.0 mEq/L) is demonstrated by repeat serum potassium determinations, triamterene and hydrochlorothiazide should be discontinued and potassium chloride supplementation initiated. Less serious hypokalemia should be evaluated with regard to other coexisting conditions and treated accordingly.

Electrolyte Imbalance: Electrolyte imbalance, often encountered in such conditions as heart failure, renal disease or cirrhosis of the liver, may also be aggravated by diuretics and should be considered during triamterene and hydrochlorothiazide therapy when using high doses for prolonged periods or in patients on a salt-restricted diet. Serum determinations of electrolytes should be performed, and are particularly important if the patient is vomiting excessively or receiving fluids parenterally. Possible fluid and electrolyte imbalance may be indicated by such warning signs as: dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal symptoms.

Hypochloremia: Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Renal Stones: Triamterene has been found in renal stones in association with the other usual calculus components. Triamterene and hydrochlorothiazide should be used with caution in patients with a history of renal stones.

(See Reverse)

[redacted]

Laboratory Tests:
Serum Potassium: The normal adult range of serum potassium is 3.5 to 5.0 mEq per liter with 4.5 mEq often being used for a reference point. If hypokalemia should develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods.

Institute such measures cautiously with frequent determinations of serum potassium levels. Potassium levels persistently above 6 mEq per liter require careful observation and treatment. Serum potassium levels do not necessarily indicate true body potassium concentration. A rise in plasma pH may cause a decrease in plasma potassium concentration and an increase in the intracellular potassium concentration. Discontinue corrective measures for hypokalemia immediately if laboratory determinations reveal an abnormal elevation of serum potassium. Discontinue triamterene and hydrochlorothiazide and substitute a thiazide diuretic alone until potassium levels return to normal.
Serum Creatinine and BUN: Triamterene and hydrochlorothiazide may produce an elevated blood urea nitrogen level, creatinine level or both. This apparently is secondary to a reversible reduction of glomerular filtration rate or a depletion of intravascular fluid volume (prerenal azotemia) rather than renal toxicity; levels usually return to normal when triamterene and hydrochlorothiazide is discontinued. If azotemia increases, discontinue triamterene and hydrochlorothiazide. Periodic BUN or serum creatinine determinations should be made, especially in elderly patients and in patients with suspected or confirmed renal insufficiency.
Serum PBI: Thiazide may decrease serum PBI levels without sign of thyroid disturbance.
Parathyroid Function: Thiazides should be discontinued before carrying out tests for parathyroid function. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as bone resorption and peptic ulceration have not been seen.
Drug Interactions:
Angiotensin-converting enzyme inhibitors: Potassium-sparing agents should be used with caution in conjunction with angiotensin-converting enzyme (ACE) inhibitors due to an increased risk of hyperkalemia.
Oral hypoglycemic drugs: Concurrent use with chlorpropamide may increase the risk of severe hyponatremia.
Nonsteroidal anti-inflammatory drugs: A possible interaction resulting in acute renal failure has been reported in a few patients on triamterene and hydrochlorothiazide when treated with indomethacin, a nonsteroidal anti-inflammatory agent. Caution is advised in administering nonsteroidal anti-inflammatory agents with triamterene and hydrochlorothiazide.
Lithium: Lithium generally should not be given with diuretics because they reduce its renal clearance and increase the risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy with triamterene and hydrochlorothiazide.
Surgical considerations: Thiazides have been shown to decrease arterial responsiveness to norepinephrine (an effect attributed to loss of sodium). This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine (an effect attributed to potassium loss); consequently caution should be observed in patients undergoing surgery.
Other Considerations: Concurrent use of hydrochlorothiazide with amphotericin B or corticosteroids or corticotropin (ACTH) may intensify electrolyte imbalance, particularly hypokalemia, although the presence of triamterene minimizes the hypokalemic effect.

Thiazides may add to or potentiate the action of other antihypertensive drugs. See INDICATIONS AND USAGE for concomitant use with other antihypertensive drugs.

The effect of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary.

Triamterene and hydrochlorothiazide may raise the level of blood uric acid; dosage adjustments of antigout medication may be necessary to control hyperuricemia and gout.

The following agents given together with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia because of the potassium-sparing nature of triamterene, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium); salt substitutes (most contain substantial amounts of potassium).

Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium levels by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake.

Chronic or overuse of laxatives may reduce serum potassium levels by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene.

The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine.
Drug/Laboratory Test Interactions: Triamterene and quinidine have similar fluorescence spectra; thus, triamterene and hydrochlorothiazide will interfere with the fluorescent measurement of quinidine.
Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: Long-term studies have not been conducted with the triamterene and hydrochlorothiazide combination, or with triamterene alone.
Hydrochlorothiazide: Two-year feeding studies in mice and rats, conducted under the auspices of the National Toxicology Program (NTP), treated mice and rats with doses of hydrochlorothiazide up to 600 and 100 mg/kg/day, respectively. On a body-weight basis, these doses are 600 times (in mice) and 100 times (in rats) the Maximum Recommended Human Dose (MRHD) for the hydrochlorothiazide component of triamterene and hydrochlorothiazide capsules at 50 mg/day (or 1 mg/kg/day based on 50 kg individuals). On the basis of body-surface area, these doses are 56 times (in mice) and 21 times (in rats) the MRHD. These studies uncovered no evidence of carcinogenic potential of hydrochlorothiazide in rats or female mice, but there was equivocal evidence of hepatocarcinogenicity in male mice.
Mutagenesis: Studies of the mutagenic potential of the triamterene and hydrochlorothiazide combination, or of triamterene alone have not been performed.
Hydrochlorothiazide: Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (the Ames test); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43 to 1300 mcg/mL. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.
Impairment of Fertility: Studies of the effects of the triamterene and hydrochlorothiazide combination, or of triamterene alone on animal reproductive function have not been conducted.
Hydrochlorothiazide: Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg/day, respectively, prior to mating and throughout gestation. Corresponding multiples of the MRHD are 100 (mice) and 4 (rats) on the basis of body-weight and 9.4 (mice) and 0.8 (rats) on the basis of body-surface area.
Pregnancy: *Category C: Teratogenic Effects:*
Triamterene and Hydrochlorothiazide: Animal reproduction studies to determine the potential for fetal harm by triamterene and hydrochlorothiazide have not been conducted. However, a One Generation Study in the rat approximated triamterene and hydrochlorothiazide composition by using a 1:1 ratio of triamterene to hydrochlorothiazide (30:30 mg/kg/day); there was no evidence of teratogenicity at those doses which were, on a body-weight basis, 15 and 30 times, respectively, the MRHD, and on the basis of body-surface area, 3.1 and 6.2 times, respectively, the MRHD.

The safe use of triamterene and hydrochlorothiazide in pregnancy has not been established since there are no adequate and well-controlled st[illegible]

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fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg/day, respectively, prior to mating and throughout gestation. Corresponding multiples of the MRHD are 100 (mice) and 4 (rats) on the basis of body-weight and 9.4 (mice) and 0.8 (rats) on the basis of body-surface area.

Pregnancy: *Category C: Teratogenic Effects*

Triamterene and Hydrochlorothiazide: Animal reproduction studies to determine the potential for fetal harm by triamterene and hydrochlorothiazide have not been conducted. However, a One Generation Study in the rat approximated triamterene and hydrochlorothiazide composition by using a 1:1 ratio of triamterene to hydrochlorothiazide (30:30 mg/kg/day); there was no evidence of teratogenicity at those doses which were, on a body-weight basis, 15 and 30 times, respectively, the MRHD, and on the basis of body-surface area, 3.1 and 6.2 times, respectively, the MRHD.

The safe use of triamterene and hydrochlorothiazide in pregnancy has not been established since there are no adequate and well-controlled studies with triamterene and hydrochlorothiazide in pregnant women. Triamterene and hydrochlorothiazide should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Triamterene: Reproduction studies have been performed in rats at doses as high as 20 times the MRHD on the basis of body-weight, and 6 times the human dose on the basis of body-surface area without evidence of harm to the fetus due to triamterene.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Hydrochlorothiazide: Hydrochlorothiazide was orally administered to pregnant mice and rats during respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively. At these doses, which are multiples of the MRHD equal to 3000 for mice and 1000 for rats, based on body-weight, and equal to 282 for mice and 206 for rats, based on body-surface area, there was no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Thiazides and triamterene have been shown to cross the placental barrier and appear in cord blood. The use of thiazides and triamterene in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia and possible other adverse reactions which have occurred in the adult.

Nursing Mothers: Thiazides and triamterene in combination have not been studied in nursing mothers. Triamterene appears in animal milk; this may occur in humans. Thiazides are excreted in human breast milk. If use of the combination drug product is deemed essential, the patient should stop nursing.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse effects are listed in decreasing order of frequency; however, the most serious adverse effects are listed first regardless of frequency. The serious adverse effects associated with triamterene and hydrochlorothiazide capsules have commonly occurred in less than 0.1% of patients treated with this product.

Hypersensitivity: anaphylaxis, rash, urticaria, photosensitivity.

Cardiovascular: arrhythmia, postural hypotension.

Metabolic: diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia.

Gastrointestinal: jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain.

Renal: acute renal failure (one case of irreversible renal failure has been reported), interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment.

Hematologic: leukopenia, thrombocytopenia and purpura, megaloblastic anemia.

Musculoskeletal: muscle cramps.

Central Nervous System: weakness, fatigue, dizziness, headache, dry mouth.

Miscellaneous: impotence, sialadenitis.

Thiazides alone have been shown to cause the following additional adverse reactions:

Central Nervous System: paresthesias, vertigo.

Ophthalmic: xanthopsia, transient blurred vision.

Respiratory: allergic pneumonitis, pulmonary edema, respiratory distress.

Other: necrotizing vasculitis, exacerbation of lupus.

Hematologic: aplastic anemia, agranulocytosis, hemolytic anemia.

Neonate and Infancy: thrombocytopenia and pancreatitis – rarely, in newborns whose mothers have received thiazides during pregnancy.

OVERDOSAGE: Electrolyte imbalance is the major concern (See WARNINGS section). Symptoms reported include: polyuria, nausea, vomiting, weakness, lassitude, fever, flushed face and hyperactive deep tendon reflexes. If hypotension occurs, it may be treated with pressor agents such as norepinephrine to maintain blood pressure. Carefully evaluate the electrolyte pattern and fluid balance. Induce immediate evacuation of the stomach through emesis or gastric lavage. There is no specific antidote.

Reversible acute renal failure following ingestion of 50 tablets of a product containing a combination of 50 mg triamterene and 25 mg hydrochlorothiazide has been reported.

Although triamterene is largely protein-bound (approximately 67%), there may be some benefit to dialysis in cases of overdosage.

DOSAGE AND ADMINISTRATION: The usual dose of triamterene and hydrochlorothiazide capsules 37.5 mg/25 mg is one or two capsules given once daily, with appropriate monitoring of serum potassium and of the clinical effect. (See WARNINGS, Hyperkalemia.)

HOW SUPPLIED: Capsules containing 37.5 mg triamterene and 25 mg hydrochlorothiazide are available for oral administration as white capsules imprinted GG 606 in black ink in bottles of 100 and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light.

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Rev. 97-3M
7188-4

C97/4

Manufactured By
Geneva Pharmaceuticals, Inc
Broomfield, CO 80020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074857

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3

2. ANDA 74-857

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

4. LEGAL BASIS FOR SUBMISSION see next page

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Triamterene and Hydrochlorothiazide Capsules, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

10. PHARMACOLOGICAL CATEGORY Diuretics

11. Rx or OTC Rx

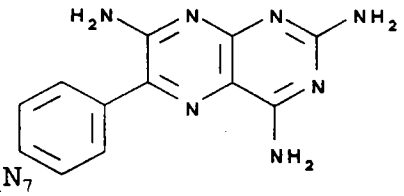
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM Capsules

14. POTENCY 37.5/25 mg

15. CHEMICAL NAME AND STRUCTURE

Triamterene, USP



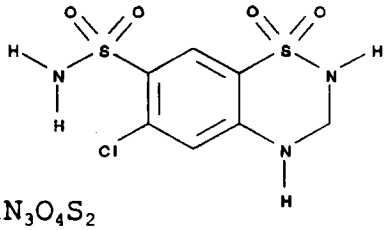
$C_{12}H_{11}N_7$

M.W. = 253.27

CAS [*396-01-1*]

2,4,7-Triamino-6-phenyl-pteridine

Hydrochlorothiazide, USP



$C_7H_8ClN_3O_4S_2$

M.W. = 297.73

CAS [*58-93-5*]

6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

16. RECORDS AND REPORTS N/A

17. COMMENTS see next page

18. CONCLUSIONS AND RECOMMENDATIONS **Recommend: APPROVAL.**

19. REVIEWER: J. L. Smith DATE COMPLETED: May 30, 1997
June 17, 1997

cc: ANDA 74-808
DUP Jacket
Division File

Endorsements:
HFD-623/J.Smith/ 6/19/97 6/18/97.
HFD-623/V.Sayeed/
Y:\NEW\FIRMSAM\GENEVA\LTRS&REV\74857AP3.CD
F/T by

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074857

BIOEQUIVALENCE REVIEW(S)

ANDA 74-857

Geneva Pharmaceuticals Inc.
U.S. Agent for: Ciba Pharmaceuticals, Inc.
Attention: Ms. Beth Brannan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

MAY 20 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Triamterene-Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/s/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

D N

MAY 16 1997

Triamterene-Hydrochlorothiazide
37.5 mg/25 mg Capsules
ANDA 74-857
Reviewer: Man M. Kochhar
74-857D.497

Geneva Pharmaceuticals, Inc.
Broomfield, Colorado
Submission Date:
November 27, 1996

Review of an Amendment

I. BACKGROUND

The sponsor had submitted a bioequivalence study and dissolution data for their triamterene-hydrochlorothiazide 37.5 mg/25 mg capsules on February 14, 1996. The bioequivalence study was acceptable but the dissolution was unacceptable to the Division of Bioequivalence. Therefore, the application was incomplete.

COMMENTS:

1. At the time of original review (February 14, 1996), the sponsor submitted dissolution data which was outside the specification of USP XXIII. USP XIII allows two dissolution methods for triamterene:hydrochlorothiazide capsules, Test 1 and Test 2. The sponsor may select anyone of those methods provided they mention in the label that the product meets USP XXIII Dissolution Test 1 or 2. The sponsor used a different dissolution method, instead of the USP XXIII method .

2. USP XXIII, Supplement 5 (Published on November 15, 1996) lists another (Test 3) dissolution method. The firm's dissolution method which is the same as the USP XXIII, Supplement 5, meets the specification of this test. Therefore, the Division of Bioequivalence concurs with the sponsor and accepts the dissolution provided by the firm in the original submission.

3. The in-vivo bioequivalence study and in-vitro dissolution testing are acceptable to the Division of Bioequivalence and therefore study is acceptable.

RECOMMENDATIONS:

1. The fasting and non-fasting bioequivalence studies conducted by Geneva on its Triamterene/Hydrochlorothiazide 37.5 mg/25 mg capsule, lot # 6495057, comparing it to Dyazide 37.5 mg/25 mg capsule, lot # 224E50, manufactured by Smith Kline have been found acceptable to the Division of Bioequivalence. The studies demonstrate that under fasting and non-fasting conditions the Geneva's Triamterene/Hydrochlorothiazide 37.5 mg/25 mg capsules are bioequivalent to the reference product, Dyazide 37.5 mg/25 mg capsules manufactured by Smith Kline.

2. In vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.1 N HCl, at 37° C using USP XXIII, (Supplement 5, Test 3) apparatus 1 (Basket) at 100 rpm. The test should meet the following specifications:

> Not less than (Q) of the labeled amount of Triamterene and Hydrochlorothiazide are dissolved in 45 minutes.

3. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution test. And therefore, the study is acceptable.

The firm should be informed of the recommendations.

Man M.Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

5/8/97
Ramakant M. Mhatre, Ph.D.
Chief, Review Branch III

Concur: _____ Date: 5/16/97
Nicholas M. Fleischer, Ph.D
Director
Division of Bioequivalence

MMKochhar/mmk/4-22-97; 4-28-97; 5-6-97; Bio 74-857

cc: ANDA # 74-857 original, HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Kochhar), Drug File, Division File.

TABLE 12

DISSOLUTION

USP XXIII :	**Apparatus 1 (Basket)**
RPM :	**100**
Number of Units:	**12**
Medium:	**900 mL of 0.1 N HCl**
Specifications:	**NLT in 45 minutes**
Reference Drug:	**Dyazide**

RESULTS

Triamterene

Time minutes	**Test Product Lot # 6495057 Strength 37.5 mg/ 25 mg**			**Reference Product Lot # 224E50 Strength 37.5 mg/25 mg**		
	Mean	Range	RSD%	Mean	Range	RSD%
15	88		4.5	80		6.9
30	97		3.7	93		3.2
45	99		3.5	97		2.5
60	100		3.7	99		1.8
HCTZ						
15	89		4.3	84		6.1
30	96		3.6	94		2.9
45	97		3.7	96		1.9
60	98		3.6	97		1.8

SEP 11 1996

Triamterene-Hydrochlorothiazide
37.5 mg/25 mg Capsules
74-857
Reviewer: Man M. Kochhar
74857.296

Ciba Pharmaceuticals, Inc.
Summit, New Jersey
Submission Date:
February 14, 1996

REVIEW OF BIOEQUIVALENCE STUDY AND DISSOLUTION DATA FASTING AND NON-FASTING

I. BACKGROUND

The sponsor has submitted a bioequivalence study with their triamterene-hydrochlorothiazide 37.5 mg/25 mg strength in thirty-two subjects. **Eventhough the lot numbers in the application the refered to Geneva the application was submitted by Ciba.**

Triamterene-hydrochlorothiazide is an orally active combination drug which is indicated for the treatment of mild-to-moderate hypertension and edema. Hydrochlorothiazide is a diuretic of the thiazide class, while triamterene is a potassium sparing agent. Triamterene is extensively metabolized to the pharmacologically active hydroxytriamterene sulfate. The plasma concentration of the metabolite is on the order of 10 times greater than that of the parent compound, and the metabolite is of primary importance to the therapeutic effect.

After oral administration, rapid absorption occurs with peak blood levels at about 1 hour. The presence of food increases the mean bioavailability of triamterene by about 67% and p-hydroxytriamterene by 50%.

Hydrochlorothiazide is a benzothiadiazide diuretic-antihypertensive. After oral administration of hydrochlorothiazide, onset of diuresis occurs in two hours and the peak effect at about 4 hours. The mean plasma half-life in fasted individuals is approximately 2.5 hours.

II. OBJECTIVE

The objective of this study is to compare the relative bioavailability of triamterene/hydrochlorothiazide 37.5 mg/25 mg (Geneva Pharmaceuticals) capsules with that of Dyazide New Formulation 37.5 mg/25 mg (Smith Kline Beecham) capsules in healthy subjects under fasting and non-fasting conditions.

III. STUDY CENTER

The bioequivalence study was conducted at and at under the supervision of

IV. STUDY DESIGN

STUDY # 1 (FASTING)

The study was a single-dose, randomized, two-way crossover bioequivalence study in fasting volunteers.

STUDY # 2 (NON-FASTING)

The study was a randomized, single-dose, three-way crossover bioequivalence study in non-fasting subjects.

Subjects:

Study # 1 employed thirty-two (32) (fasting condition) and Study # 2 employed 18 (non-fasting) healthy male volunteers between 18 and 40 years of age whose weight did not deviate by more than 10% of the ideal for their height and age (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Volunteers without history of asthma, nasal polyps, or serious cardiovascular, hepatic, renal, hematopoietic, peptic ulcer or gastrointestinal disease, alcohol or drug abuse were employed.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, and urinalysis). Subjects were not allowed to take any medication for 7 days prior to the study and to refrain from consumption of alcoholic or caffeine containing foods and beverages from 48 hours prior to dosing until study completion.

Vital sign measurements including heart rate, blood pressure, respiration, and temperature were recorded on admission to the study unit on Day 0 and 7, and at pre-dose on Day 1 and 8. In addition, heart rate and blood pressure only were recorded at approximately 1, 6, 12, and 24 hours post dose administration. Vital sign measurements were obtained from the subjects in the sitting position.

The subjects were housed in the Clinic from 12 hours before until 24 hours after the drug administration. The subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 1 hour of the drug administration.

In non-fasting study the subjects fasted for 10 hours. The drug was administered 20 minutes after standard breakfast. Subjects were instructed to eat their entire meal in the time allotted. The first subsequent meal was served 4 hours after dosing.

Methods

The product and dosage employed in study #1 were as follows:

FASTING

Treatments A: Test: 1 x 25 mg/37.5 mg hydrochlorothiazide/triamterene capsule, lot # 6495057, administered with 240 mL of water.
Batch Size: Expiry Date: 8/97
Potency: 95.1% (triamterene); 98.4% HCTZ
Content Uniformity: 95.8% (triamterene); 93.6% HCTZ

Treatment B: Reference: 1 x 25 mg/37.5 mg Dyazide, New Formulation capsule (Smith Kline Beecham),lot # 224E50 administered with 240 mL of water.
Expiry Date: 6/96
Potency: 96.4% (triamtrene); 100.0% HCTZ
Content Uniformity: 99.8 (triamterene); 95.2% HCTZ

STUDY # 2

NON-FASTING

The product employed in this study were:

Treatment C: Test: One 25 mg/37.5 mg, hydrochlorothiazide/triamterene capsule,(lot # 6495057) with 240 mL of water (Fasting).

Treatment D: Test: one 25 mg/37.5 mg, hydrochlorothizide/triamterene capsule,(lot# 6495057) with 240 mL of water (non-fasting)

Treatment E: Reference: one 25 mg/37.5 mg Dyazide (Smith Kline Beecham) capsule,(lot # 224E50) with 240 mL of water (non-fasting).

In study # 1 subjects fasted for 10 hours prior to and 4 hours after drug administration. The subjects consumed 240 mL of water one hour before dosing. Water was permitted ad lib. until 1 hour before dosing and again at 1 hours after dosing.

In study # 2 (non-fasting) subjects fasted overnight until 20 minutes prior to their schedule dosing times, when they were given a standard breakfast.

Blood Samples:

Triamterene and Hydrochlorothiazide

14 mL of blood samples were collected in Vacutainers containing EDTA, at 0, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, and 48 hours, following drug administration. The zero hour blood draw was taken before dosing. The blood was centrifuged and plasma separated and frozen immediately.

A urine sample (bladder completely emptied) was obtained from each subject prior to dosing.

All urine voided from each subject was retained in a clean container over these collection intervals: 0, 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-24, 24-36, and 36-48 hours after dosing.

The urine samples (pre-dose and for each interval) were accurately measured for total volume. The samples were stirred, and a 20 mL aliquot saved in a plastic (polypropylene) container. The aliquots were frozen until analyzed.

Washout Period: 1 week between doses.

Analytical Methodology:

Assay Validation:

Triamterene

pages 5 and 6 REMOVED
CONTAIN CONFIDENTIAL COMMERCIAL AND
TRADE SECRET INFORMATION

DATA ANALYSIS

Individual analysis of variance (ANOVA with factors including drug, phase, sequence and subjects within sequence) were carried out to compare formulations at each sampling time, AUC_{0-t}, AUCinf, C_{max}, T_{max}, $t_{1/2}$ and K_{el}. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test) were calculated for hydrochlorothiazide, triamterene and p-hydroxytriamterene sulfate pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Of the 32 subjects enrolled in the study, 30 completed the study. Subject # 28 dropped prior to period 2 dosing for personal reasons and Subject # 12 dropped after sample collection 7 of the period 2. The data for 30 subjects were analyzed for triamterene, hydroxytriamterene and hydrochlorothiazide as proposed in the protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of triamterene, hydroxytriamterene and hydrochlorothaiazide are given in Tables 1, 2, 3, 4, 5 and 6. The mean plasma triamterene and hydroxytriamterene concentrations are given in Figure 1 and 2 and urine hydrochlorothiazide in Figure 3.

TABLE 1

Mean Plasma Concentration of Triamterene (N=30)

Time (hours)	Geneva's Product Lot # 6495057 ng/mL (CV%)	Smith Kline's Dyazide Lot # 224E50 ng/mL (CV%)	T/R
0	0.0 (--)	0.0 (---)	0.0
0.33	20.2 (107)	30.9 (95)	0.65
0.5	42.2 (46)	56.8 (67)	0.74
0.75	65.1 (48)	71.7 (51)	0.91
1	67.9 (40)	71.8 (43)	0.94
1.25	65.6 (38)	70.3 (38)	0.93
1.5	63.7 (38)	66.9 (34)	0.95
2	54.9 (38)	54.3 (35)	1.01
3	36.1 (41)	35.6 (38)	1.01
4	24.3 (42)	23.3 (39)	1.04
6	10.1 (44)	9.8 (41)	1.03
8	4.9 (49)	4.9 (46)	1.00
10	2.2 (85)	1.9 (100)	1.15
12	0.68 (171)	0.56 (208)	1.21
14	0.07 (547)	0.17 (380)	0.41
24	0.00 (---)	0.00 (---)	0.00
36	0.00 (---)	0.00 (---)	0.00
48	0.00 (---)	0.00 (---)	0.00

Table 2

A Summary of Triamterene Pharmacokinetic Parameters for 30 subjects

Parameters	Geneva's Triamterene/HCTZ	SmithKline's Dyazide	T/R	90% Confidence Interval
AUC_{0-48} ng.h/mL	234.4 (34)	241.2 (36)	0.97	89; 106
AUC_{0-inf} ng.hr/mL	241.6 (33)	248.8 (35)	0.97	89; 105

C_{max} ng/mL	81.6 (36)	84.6 (36)	0.96	84; 109
T_{max} (hours)	1.04 (40)	0.97 (43)	1.07	
$t_{1/2}$ (hours)	1.83 (16)	1.81 (18)	1.01	
K_{el} (1/hour)	0.389 (16)	0.392 (15)	0.99	
Ln AUCo-t ng.hr/mL	5.39 (7)	5.42 (7)		88; 108
Ln AUCinf ng.hr/mL	5.43 (6)	5.45 (7)		88; 107
LnCmax ng/mL	4.33 (9)	4.36 (9)		84; 110

TABLE 3

Mean Plasma Concentration of Hydroxytriamterene (N=30)

Time (hours)	**Geneva's Triamterene/HCTZ ng/mL (CV%)**	**SmithKline's Dyazide ng/mL (CV%)**	**T/R**
0	0.0 (---)	0.0 (---)	0.0
0.33	94.1 (161)	135.3 (115)	0.69
0.50	399.6 (80)	529.5 (70)	0.75
0.75	835.9 (51)	973.4 (45)	0.86
1	984.4 (44)	1075.7 (35)	0.91
1.25	981.1 (40)	1063.7 (31)	0.92
1.50	931.4 (38)	1006.1 (29)	0.92
2	769.2 (37)	787.4 (30)	0.98
3	424.3 (40)	435.8 (33)	0.97
4	252.9 (39)	256.4 (33)	0.99
6	132.8 (37)	135.4 (31)	0.98

8	66.2 (38)	67.9 (32)	0.97
10	37.1 (35)	37.9 (31)	0.98
12	23.2 (34)	23.9 (32)	0.97
14	14.4 (61)	16.1 (50)	0.89
24	4.9 (155)	4.9 (163)	1.00
36	1.9 (261)	1.9 (277)	1.00
48	0.9 (380)	0.6 (547)	1.50

TABLE 4

A Summary of Hydroxytriamterene Pharmacokinetic Parameters for 30 Subjects

Parameters	Geneva's Triamterene/HCTZ	SmithKline's Dyazide	T/R	90% Confidence Interval
AUC_{o-t} ng.hr/mL	3166.6 (28)	3355.6 (24)	0.94	90; 99
AUC_{inf} ng.hr/mL	3333.2 (28)	3508.8 (24)	0.95	91; 98
C_{max} ng/mL	1117.5 (37)	1221.0 (28)	0.91	82; 101
T_{max} hours	1.3 (37)	1.2 (33)	1.08	
$t_{1/2}$ hours	8.9 (157)	8.1 (120)	1.09	
K_{el} 1/hour	0.200 (57)	0.192 (59)	1.04	
$LnAUC_{o-t}$ ng.hr/mL	8.0 (4)	8.1 (4)		89; 98
$LnAUC_{inf}$ ng.hr/mL	8.1 (4)	8.1 (4)		91; 98
LnC_{max} ng/mL	6.9 (6)	7.0 (5)		80; 99

TABLE 5

Urine Data of Hydrochlorothiazide (N=30)

Time (hours)	Geneva's Triamterene/HCTZ Urine HCTZ in mg (CV%) over Collection Interval	SmithKline's Dyazide Urine HCTZ in mg (CV%) over Collection Interval		T/R
0	0.00 (---)	0.00 (---)		0.0
0-2	1.95 (51)	2.73 (47)		0.71
2-4	5.26 (24)	5.71 (31)		0.92
4-6	3.07 (29)	3.11 (34)		0.99
6-8	1.62 (38)	1.51 (29)		1.07
8-10	1.16 (21)	1.01 (30)		1.15
10-12	0.83 (27)	0.84 (18)		0.99
12-14	0.50 (67)	0.54 (67)		0.92
14-24	1.66 (34)	1.64 (35)		1.01
24-36	0.00 (---)	0.09 (547)		0.00
36-48	0.00 (---)	0.00 (---)		0.00
cumulative excretion				
0	0.00 (---)	0.00 (---)		0.00
0-2	1.93 (51)	2.73 (47)		0.71
0-4	7.21 (26)	8.43 (27)		0.86
0-6	10.29 (20)	11.55 (20)		0.89
0-8	11.91 (19)	13.01 (19)		0.91
0-10	13.01 (17)	14.12 (18)		0.92
0-12	13.89 (17)	14.96 (18)		0.93
0-14	14.39 (18)	15.50 (18)		0.93
0-24	16.01 (17)	17.14 (18)		0.93
0-36	16.01 (17)	17.23 (18)		0.93
0-48	16.01 (17)	17.23 (18)		0.93
			90% Confidence Interval	
CUM_{0-48}	16.01 (17)	17.23 (18)	88 to 98	0.93
R_{max}	2.68 (22)	2.95 (27)	84 to 97	0.91
T_{max}	3.13 (16)	3.01 (12)	98 to 106	1.04
$LnCUM_{0-48}$	2.76	2.83	88 to98	

CUM_{0-48}----------Total cumulative excretion from time 0 to 48 hours in mg.
R_{max} ----------Maximum excretion rate in mg/hour
T_{max} ----------Time (hours) to maximum excretion rate

The triamterene AUC_{0-48} and AUC_{inf} produced by Geneva's formulation are 2.81.lower and 2.89% lower respectively than the values for the reference drug. The C_{max} is 3.54% lower for test than the reference. T_{max} was 7.2% higher for the test drug. $t_{1/2}$ and K_{el} values differ only by less than 1.1%. ANOVA performed on the plasma triamterene concentration data at each of the seventeen sampling times detected no statistically significant differences at any time point between the two formulations. The test to reference ratios are 0.97 for AUC (0-48), 0.97 for AUCinf, 0.96 for Cmax, and 1.07 for Tmax.

The 90% confidence interval for AUC_{0-48}, AUC_{inf} and C_{max} were well within 20% limits set for defining product bioequivalence, in a fasting study. The 90% confidence intervals for $LnAUC_{0-48}$ was 88 to 108, for $LnAUC_{inf}$ was 88 to 107 and for LnC_{max} 84 to 110.

The p-hydroxytriamterene AUC_{0-48} and AUC_{inf} produced by Geneva's formulation are 5.6% lower and 5.0% lower respectively than the values for the reference drug. The C_{max} is 8.4% lower for the test than the reference. Tmax was 8.3% higher for the test drug. $t_{1/2}$ and K_{el} were 9.9% and 4.1% higher respectively than the reference drug. ANOVA performed on the plasma p-hydroxytriamterene concentration data at each of the 17 sampling times detected no statistically significant differences at any time point between the two formulations. The test to reference ratios are 0.94 for AUC(0-48), 0.95 for AUCinf, 0.91 for Cmax and 1.08 for Tmax.

The 90% confidence interval for AUC_{0-48}, AUC_{inf} and C_{max} were well within 20% limits set for defining product bioequivalence, in a fasting study. The 90% confidence intervals for $LnAUC_{0-48}$ was 89 to 98, for $LnAUC_{inf}$ was 91 to 98 and for LnC_{max} was 80 to 99.

HYDROCHLOROTHIAZIDE

The total cumulative excretion of hydrochlorothiazide for Geneva's product was 16.1 mg and for reference drug it was 17.23 mg. The CUM_{0-48} was 6.5% lower for the test product and the maximum rate (R_{max}) was 3.4% lower for the test drug. The T_{max} was 3.9% higher for the test drug.

The 90% confidence intervals for CUMo-t was 88 to 98, for Rmax was 84 to 97 and for Tmax was 98 to 106. The confidence interval for LnCUMo-48 was 88 to 98.

Twenty-two adverse events were reported and these were dizziness (2), headache (8), malaise (1), nausea (1), pharyngitis (4), respiratory disorder (2), rhinitis (3), and vomiting (1). There were no serious adverse events which required terminating any subject from the study.

On the basis of fasting in-vivo bioavailability data it is determined that Geneva's triamterene/hydrochlorothiazide 37.5 mg/25 mg capsules and Smith Kline's Dyazide capsules are bioequivalent under fasting conditions.

NON-FASTING STUDY:

Of the 18 subjects enrolled in the study, 17 completed the crossover. One subject # 7 dropped prior to Period 3 dosing due to scheduling conflict.The statistical analysis were performed on data from 17 subjects as described in the protocol. The mean plasma levels and the pharmacokinetic parameters of triamterene , p-hydroxytriamterene and urine hydrochlorothiazide for 17 subjects under non-fasting conditions are summarized in Tables 6,7,8,9, and 10. The mean plasma concentrations of triamterene, p-hydroxytriamterene and hydrochlorothiazide are given in Figures 4, 5, and 6.

TABLE 6

MEAN PLASMA CONCENTRATIONS OF TRIAMTERENE (N=17)

Time (hours)	Geneva's Triamterene/HCTZ Lot #6495057 Treat. C ng/mL (CV%) Fasting	Treat. D ng/mL (CV%) Non-fasting	Smith Kline's Dyazide Lot #224E50 Treat. E ng/mL (CV%) Non-fasting	T/R Tr. D/Tr. E
0.0	0.00	0.00	0.00	0.00
0.33	25.6 (97)	0.5 (287)	0.9 (201)	0.55
0 50	54.1 (66)	2.0 (156)	2.6 (172)	0.77
0.75	68.6 (56)	6.4 (121)	5.5 (129)	1.16
1.0	67.7 (45)	12.0 (93)	11.0 (109)	1.09
1 25	71.1 (35)	24.4 (67)	22.6 (90)	1.07
1.5	73.6 (52)	34.7 (55)	36.0 (66)	0.96
2.0	59.9 (48)	45.0 (39)	47.7 (48)	0.94
3.0	39.7 (48)	50.1 (26)	58.0 (31)	0.86
4.0	26.6 (52)	44.9 (24)	52.2 (31)	0.86
6.0	11.8 (57)	21.2 (36)	26.0 (16)	0.81
8.0	6.3 (60)	9.8 (44)	11.9 (48)	0.82
10.0	3.1 (84)	5.0 (61)	5.7 (13)	0.88
12.0	1.4 (120)	2.4 (129)	2.6 (75)	0.92
14.0	0.5 (226)	0.7 (318)	0.6 (226)	1.16
24.0	0.0 (---)	0.3 (412)	0.0 (------)	0.00
36.0	0.0 (---)	0.0 (----)	0.0 (-----)	0.00
48.0	0.0 (---)	0.0 (----)	0.0 (----)	0.00

TABLE 7

A SUMMARY OF TRIAMTERENE PHARMACOKINETIC PARAMETERS FOR 17 SUBJECTS

Parameters	Geneva's Triamterene/HCTZ. (CV%)		Smith Kline's Dyazide (CV%)	Treat. D/ Treat. E	90% Confidence Intervals
	Treat C	Treat D	Treat. E		
AUC_{0-48} ng.hr/mL	265.2 (39)	254.7 (26)	287.4 (28)	0.89	79; 98
AUC_{0-inf} ng.hr/mL	273.8 (38)	265.4 (27)	295.9 (28)	0.89	80; 99
C_{max} ng/mL	91.7 (43)	57.2 (20)	65.3 (25)	0.87	67; 108
T_{max} hours	0.98 (35)	2.8 (35)	3.0 (33)	0.93	
$t_{1/2}$ hours	2.1 (31)	2.2 (18)	1.9 (13)	1.16	
K_{el} 1/hr	0.348 (15)	0.363 (24)	0.371 (14)	0.98	
				Ratio of Geo-metric Means	
LnAUCo-48 ng.hr/mL	5.50 (8)	5.50 (5)	5.62 (5)	88.8%	80; 99
LnAUCinf ng.hr/mL	5.54 (7)	5.54 (5)	5.65 (5)	89.6%	81; 99
LnCmax ng/mL	4.43 (10)	4.02 (5)	4.15 (6)	88.3%	75; 104

Fasting-Non-fasting Comparison (Treat. C vs D) Geneva:

The ratio of means for untransformed parameters were 1.04 and 1.03 for AUCo-t and AUCinf,

respectively. The Cmax ratio was 1.60. The mean Tmax was 0.98 hours under fasting conditions and 2.8 hours under non-fasting conditions.

Non-Fasting Comparison (Treatment D vs Treatment E) Geneva vs Smith Kline:

The ratio of means (D/E) for the untransformed parameters, AUCo-t, AUCinf and Cmax were 0.88, 0.89 and 0.87 respectively. Mean Tmax values were 2.8 hours and 3.0 hours for Geneva (Treatment D) and Smith Kline (Treatment E) products, respectively. The ratios for t1/2 and Kel were 1.16 and 0.98 respectively. The ratios for log transformed parameters LnAUCo-t, LnAUCinf, and LnCmax were 88.8%, 89.6% and 88.3% respectively.

The mean plasma concentration showed statistically significant differences at 0.33 and 0.50 hours. The ratios of geometric means were between 0.8 to 1.2.

TABLE 8

MEAN PLASMA CONCENTRATION OF HYDROXYTRIAMTERENE (N=17)

Time (hours)	Geneva's Triamterene/HCTZ Lot #6495057 Treat. C ng/mL(CV%) Fasting	Treat D ng/mL(CV%) Non-fasting	Smith Kline's Dyazide Lot # 224E50 Treat E ng/mL(CV%) Non-fasting	T/R Tr D/ Tr E
0.00	0.00 (---)	0.00 (----)	0.00 (----)	0.00
0.33	88.11 (113)	1.98 (295)	0.79 (412)	2.50.
0.50	397.63 (69)	10.52 (169)	15.57 (213)	0.67
0.75	783.27 (59)	49.12 (124)	47.23 (130)	1.04
1.00	880.77 (47)	110.45 (93)	98.57 (99)	1.12
1.25	874.53 (37)	219.09 (75)	189.65 (92)	1.15
1.50	855.06 (27)	386.64 (62)	342.41 (66)	1.12
2.00	724.71 (38)	604.94 (44)	573.57 (45)	1.05
3.00	410.71 (38)	702.53 (27)	732.47 (26)	0.96
4.00	256.22 (38)	585.76 (28)	594.00 (26)	0.98
6.00	131.71 (37)	262.47 (34)	295.82 (31)	0.89
8.00	67.04 (36)	117.48 (34)	128.21 (31)	0.92
10.00	37.92 (31)	60.92 (44)	65.04 (35)	0.94
12.00	24.54 (30)	35.39 (65)	34.92 (34)	1.01
14.00	15.89 (50)	20.61 (85)	19.51 (41)	1.05
24.00	3.36 (188)	2.69 (412)	0.00 (---)	0.00
36.00	0.00 (---)	0.00 (----)	0.00 (---)	0.00
48.00	0.00 (----)	0.00 (---)	0.00 (----)	0.00

TABLE 9

A SUMMARY OF HYDROXYTRIAMTERENE PHARMACOKINETIC PARAMETERS FOR 17 SUBJECTS

Parameters	Geneva's Triamterene/ HCTZ (CV%) Treat C Fasting	Treat D Non-fasting	Smith Kline's Dyazide (CV%) Treat E Non-fasting	Treat D/ Treat E	90% Confidence Intervals
AUC_{0-48} ng.hr/mL	2979.3 (22)	3292.7 (16)	3334.9 (16)	0.99	94; 104
AUC_{inf} ng.hr/mL	3070.0 (20)	3374.2 (16)	3401.0 (16)	0.99	94; 104
C_{max} ng/mL	1043.8 (31)	781.8 (24)	794.3 (21)	0.98	85; 112
T_{max} hours	1.2 (37)	2.96 (22)	2.96 (33)	1.00	
$t_{1/2}$ hours	4.1 (101)	2.37 (58)	2.15 (8)	1.10	
K_{el} 1/hr	0.248 (37)	0.327 (20)	0.334 (8)	0.98	
				Ratio of Geo-metric Means	
$LnAUC_{0-48}$ ng.hr/mL	7.97 (3)	8.09 (2)	8.09 (2)	100.0%	93; 105
$LnAUC_{inf}$ ng.hr/mL	8.01 (3)	8.11 (2)	8.12 (2)	99.2%	94; 104
LnC_{max} ng/mL	6.90 (5)	6.63 (4)	6.66 (3)	97.8%	87; 110

Fasting-Nonfasting Comparison (Treat. C vs D) Geneva:

The ratios of means for untransformed parameters were 0.99 for AUCo-t and AUCinf and for

Cmax ratio was 0.98. The mean Tmax was 1.2 hours under fasting condition and 2.96 hours under non-fasting condition.

Non-Fasting Comparison (Treatment D vs E) Geneva vs Smith Kline

The ratio of means (D/E) for the untransformed parameters, the AUCo-t, AUCinf, and Cmax were 0.99, 0.99 and 0.98 respectively. Mean Tmax values were same for both products. The ratios for t1/2 and Kel were 1.10 and 0.98 respectively. The ratios for log-transformed parameters AUCo-t, AUCinf and Cmax were 1.00, 0.99 and 0.98 respectively.

The plasma hydroxytriamterene concentration showed statistically significant differences at 0.33 and 0.5 hours.

TABLE 10

Urine Data of Hydrochlorothiazide

Time (hours)	Geneva's Triamterene/HCTZ Urine HCTZ in mg (CV%) over Collection Interval		Smith Kline Dyazide Urine HCTZ in mg (CV%) Over Collection Interval	Treat. D/ Treat. E
	Fasting (Treat. C)	Non-Fasting (Treat. D)	Non-Fasting (Treat. E)	
0	0.00 (---)	0.00 (--)	0.00 (--)	0.00
0-2	3.11 (57)	0.43 (138)	0.34 (123)	1.26
2-4	5.99 (23)	4.95 (34)	4.67 (36)	1.06
4-6	3.44 (45)	4.55 (23)	5.18 (27)	0.88
6-8	1.66 (43)	2.87 (45)	2.86 (32)	1.00
8-10	1.16 (44)	1.39 (28)	1.55 (24)	0.89
10-12	0.87 (32)	0.99 (26)	1.11 (30)	0.89
12-14	0.52 (85)	0.84 (35)	0.80 (39)	1.05
14-24	1.93 (52)	2.03 (24)	2.03 (52)	1.00
24-36	0.28 (283)	0.49 (226)	0.32 (--)	1.53
36-48	0.00 (-- -)	0.00 (--)	0.00 (--)	0.00
Cumulative Excretion				
0	0.00 (---)	0.00 (--)	0.00 (--)	0.00
0-2	3.11 (57)	0.43 (138)	0.34 (123)	1.26
0-4	9.10 (27)	5.38 (39)	5.00 (36)	1.08
0-6	12.54 (23)	9.92 (20)	10.18 (25)	0.97
0-8	14.19 (23)	12.80 (20)	13.04 (23)	0.98

0-10	15.36 (23)	14.19 (18)	14.59 (21)	0.97
0-12	16.23 (22)	15.18 (18)	15.70 (21)	0.97
0-14	16.75 (23)	16.02 (17)	16.50 (21)	0.97
0-24	18.68 (24)	18.06 (17)	18.54 (22)	0.97
0-36	18.97 (25)	18.54 (19)	18.86 (25)	0.98
0-48	18.97 (25)	18.54 (19)	18.86 (25)	0.98

				90% Confidence Intervals	
CUM_{0-48}	18.97 (25)	18.54 (19)	18.86 (25)	93; 104	0.98
R_{max}	3.08 (21)	2.80 (25)	2.79 (23)	91; 110	1.00
T_{max}	3.00 (23)	3.93 (32)	4.30 (23)	78; 105	0.91
$LnCUM_{0-48}$		2.92	2.91	94; 106	

CUM_{0-48}.....Total cumulative excretion from time 0 to 48 hours in mg
R_{max} .....Maximum excretion rate in mg/hour
T_{max} .....Time (hours) to maximum excretion rate

Non-Fasting Comparison (Treatment D vs E) Geneva vs Smith Kline

The total cumulative excretion for hydrochlorothiazide for Geneva's product was 18.54 mg and for reference product it was 18.86 mg under non-fasting condition. The CUM0-48 was 1.69% lower for the test product and the maximum rate (Rmax) was same for test and reference products. The Tmax was 8.6% lower for the test drug.

No serious clinical events were reported by the subjects.

On the basis of non-fasting in vivo bioavailability data it is determined that Geneva's Triamterene/hydrochlorothiazide 35.5 mg/ 25 mg capsules and Smith Kline's Dyazide capsules are bioequivalent.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of 0.1 N HCl, at 37°C using USP XXIII apparatus 1 (Basket) at 100 rpm. Results are presented in Table 11. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablets in 45 minutes.

The batch size was capsules.

COMMENTS:

FASTING

1. The study was conducted in 30 healthy volunteers comparing the plasma concentrations from Geneva's triamterene/HCTZ 37.5 mg/ 25 mg capsule to that of reference Dyazide, 37.5 mg/25 mg capsule manufactured by Smith Kline. The triamterene AUC_{0-48}, AUC_{0-inf}, C_{max} of the Geneva's formulation were 2.81% lower, 2.89% lower, and 3.54% lower respectively than the corresponding Smith Kline's reference values.

2. The hydroxytriamterene AUC_{0-48}, AUC_{inf} and C_{max} of the Geneva's formulation were 5.6% lower, 5.0% lower, and 8.4% lower respectively than the corresponding reference values. The 90% confidence intervals were well within the limits set by the Division of Bioequivalence. The ratios of geometric means for AUC and Cmax were within .8 to 1.2.

3. The test product CUM_{0-48}, R_{max} and T_{max} differ from the reference product by 6.5%, 3.4% and 3.9% respectively.

These results indicate that the test drug is bioequivalent to the reference product under fasting conditions.

4. Analysis of variance indicated no statistically significant treatment differences for AUC_{0-48}, AUC_{inf}. and Cmax for triamterene/hydrochlorothiazide 37.5 mg/ 25 mg capsules. The 90% confidence intervals are within 80% to 125% for all log-transformed pharmacokinetic parameters.

5. The assay validation studies conducted by the sponsor are acceptable to the Division of Bioequivalence.

6. No serious adverse reactions were observed by any subject.

7. The in vitro dissolution testing conducted for 37.5 mg/25 mg capsules of the test and reference products is not acceptable for the reasons cited under deficiency.

8. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

9. The in vivo fasting bioequivalence study for 37.5 mg/ 25 mg capsules of triamterene/HCTZ is acceptable.

NON-FASTING:

1. The triamterene ratios for AUC_{0-48}, AUC_{inf}, and C_{max} of the test to reference formulation were 0.89, 0.89 and 0.87 respectively. The ratios for these parameters were well within the limits set by the Division of Bioequivalence. The ratios of Geometric means for the log-transformed parameters were within the range of 88.6% to 89.6%. Plasma triamterene data resulted in no statistically significant differences in product for any of the pharmacokinetic parameters.

2. The hydroxytriamterene ratios for AUC_{0-48}, AUC_{inf} and C_{max} were 0.99, 0.99 and 0.98 respectively. The ratios for these parameters were well within the limits set by the Division of Bioequivalence.

3. The test product CUM_{0-48}, R_{max}, T_{max} differ by 1.69%, 0.35% and 8.6% respectively from the reference product.

4. The Geneva's and Smith Kline's Dyazide 37.5 mg/ 25 mg capsules appear to show comparable bioavailability under non-fasting conditions. The data showed that administration of triamterene/hydrochlorothiazide with food resulted in a significantly lower triamterene C max and longer Tmax.

5. No serious clinical events were recorded during this period.

6. The in vivo non-fasting bioequivalence study is acceptable to the Division of Bioequivalence.

DEFICIENCY: The dissolution conducted by the company is not acceptable to the Division of Bioequivalence. The dissolution testing should be conducted in 0.1 M acetic acid containing 1% of polysorbate 20 at 37° C using USP XXIII apparatus 2 (paddle) at 100 rpm. The dissolution should meet the following specifications:

> Not less than of the labeled amount of triamterene and hydrochlorothiazide is dissolved in 120 minutes.

RECOMMENDATIONS:

1. The fasting and non-fasting bioequivalence studies conducted by Geneva on its Triamterene/Hydrochlorothiazide 37.5 mg/ 25 mg capsule, lot # 6495057, comparing it to Dyazide 37.5 mg/ 25 mg capsule, lot # 224E50, manufactured by Smith Kline have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting and non-fasting conditions the Geneva's Triamterene/Hydrochlorothiazide 37.5 mg/25 mg capsules are bioequivalent to the reference product, Dyazide 37.5 mg/25 mg capsules manufactured by Smith Kline. However, the application is incomplete due to unacceptable dissolution studies.

2. The in vitro test results are not acceptable. The dissolution testing should be conducted in 900

mL of 0.1M acetic acid containing 1% polysorbate 20 at 37°C using USP XXIII apparatus 2 (Paddle) at 100 rpm. The test should meet the following specifications:

> Not less than of the labeled amounts of the triamterene and hydrochlorothiazide in the capsule are dissolved in 120 minutes.

The firm should be informed of the recommendations.

/ . / ,,.

Man M.Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE 8/1/96

Concur: _____ Date: 8/28/96
for Kenith K. Chan, Ph.D
Director
Division of Bioequivalence

MMKochhar/mmk/7-1-96; 7-24-96; 74-857

cc: 74-857 original, HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD-658 (Mhatre, Kochhar),Drug File, Division File.

Information not to be released under FOI

TABLE 11

FORMULATION

Ingredients	Quantity/Capsule
Triamterene, USP	37.50 mg
Hydrochlorothiazide, USP	25.00 mg
Lactose Anhydrous, NF	
Povidone, USP	
Sodium Starch Glycolate	
Glycine, USP	
Citric Acid, Anhydrous, USP	
Polysorbate 80, NF	
Magnesium Stearate, NF	
Isopropyl Alcohol, USP	
Purified Water, USP	
# 4 Opaque White Cap/ Opaque White Body, Body and Cap Imprinted	
TOTAL	200.00 mg

TABLE 12

DISSOLUTION

USP XXIII :	**Apparatus 1 (Basket)**
RPM :	**100**
Number of Units:	**12**
Medium:	**900 mL of 0.1 N HCl**
Specifications:	**NLT in 45 minutes**
Reference Drug:	**Dyazide**

RESULTS

Triamterene **Time minutes**	**Test Product Lot # 6495057 Strength 37.5 mg/ 25 mg**			**Reference Product Lot # 224E50 Strength 37.5 mg/25 mg**		
	Mean	Range	RSD%	Mean	Range	RSD%
15	88		4.5	80		6.9
30	97		3.7	93		3.2
45	99		3.5	97		2.5
60	100		3.7	99		1.8
HCTZ						
15	89		4.3	84		6.1
30	96		3.6	94		2.9
45	97		3.7	96		1.9
60	98		3.6	97		1.8

FIGURE 1

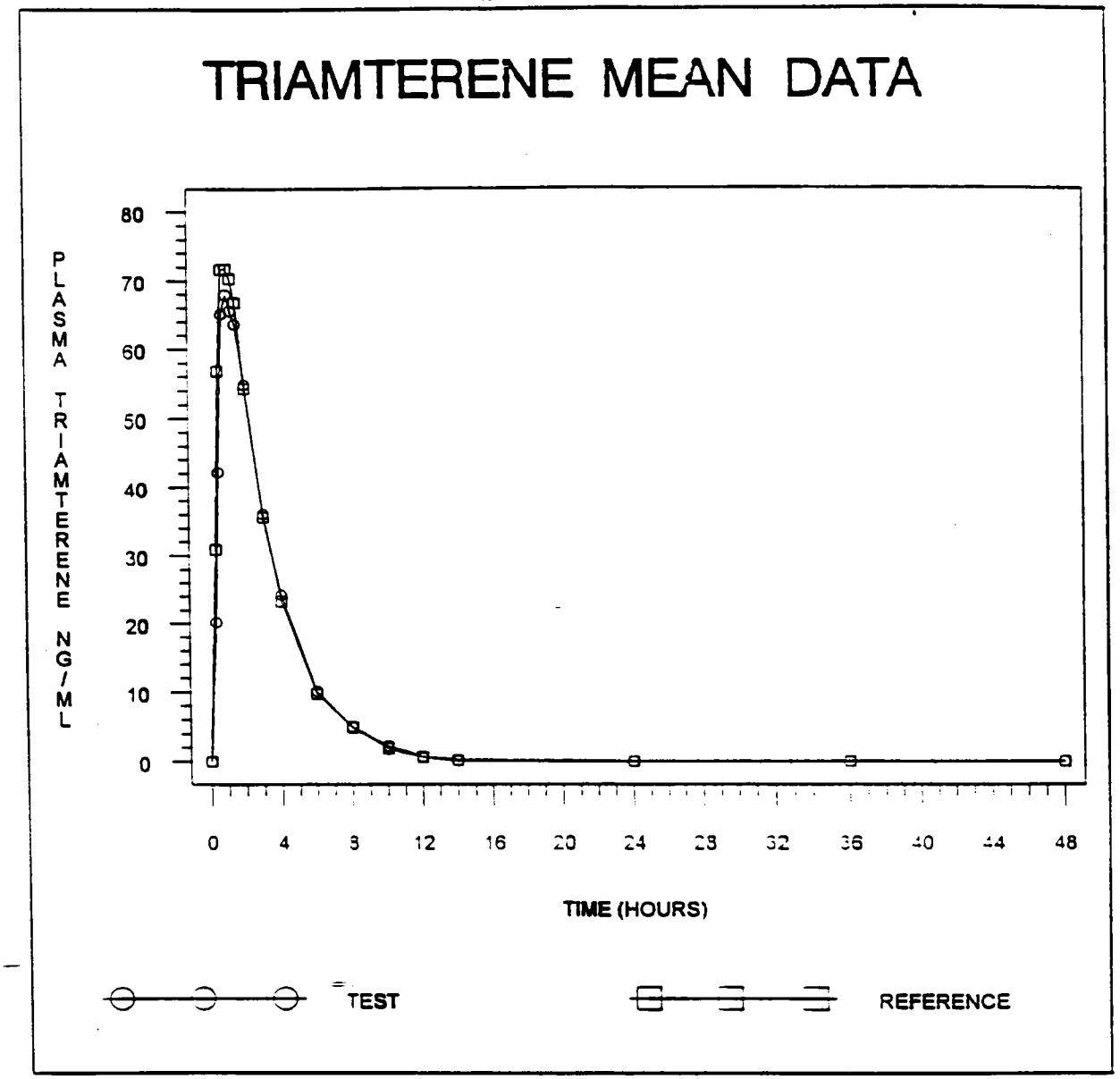

TRIAMTERENE MEAN DATA
PLASMA TRIAMTERENE NG/ML
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
28
32
36
40
44
48
TIME (HOURS)
TEST
REFERENCE

FIGURE 2

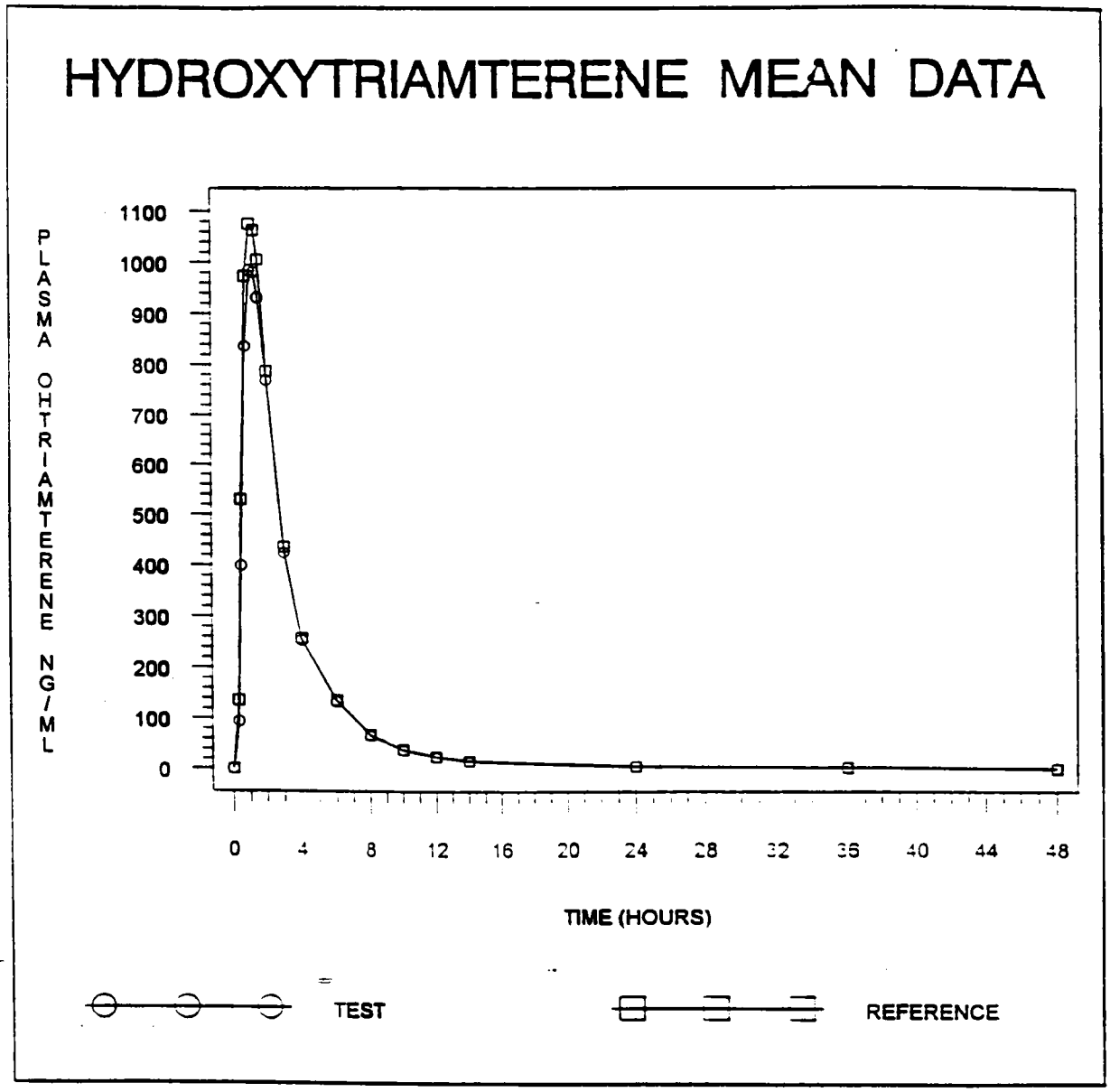

HYDROXYTRIAMTERENE MEAN DATA
PLASMA OHTRIAMTERENE NG/ML
1100
1000
900
800
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
28
32
36
40
44
48
TIME (HOURS)
TEST
REFERENCE

FIGURE 3

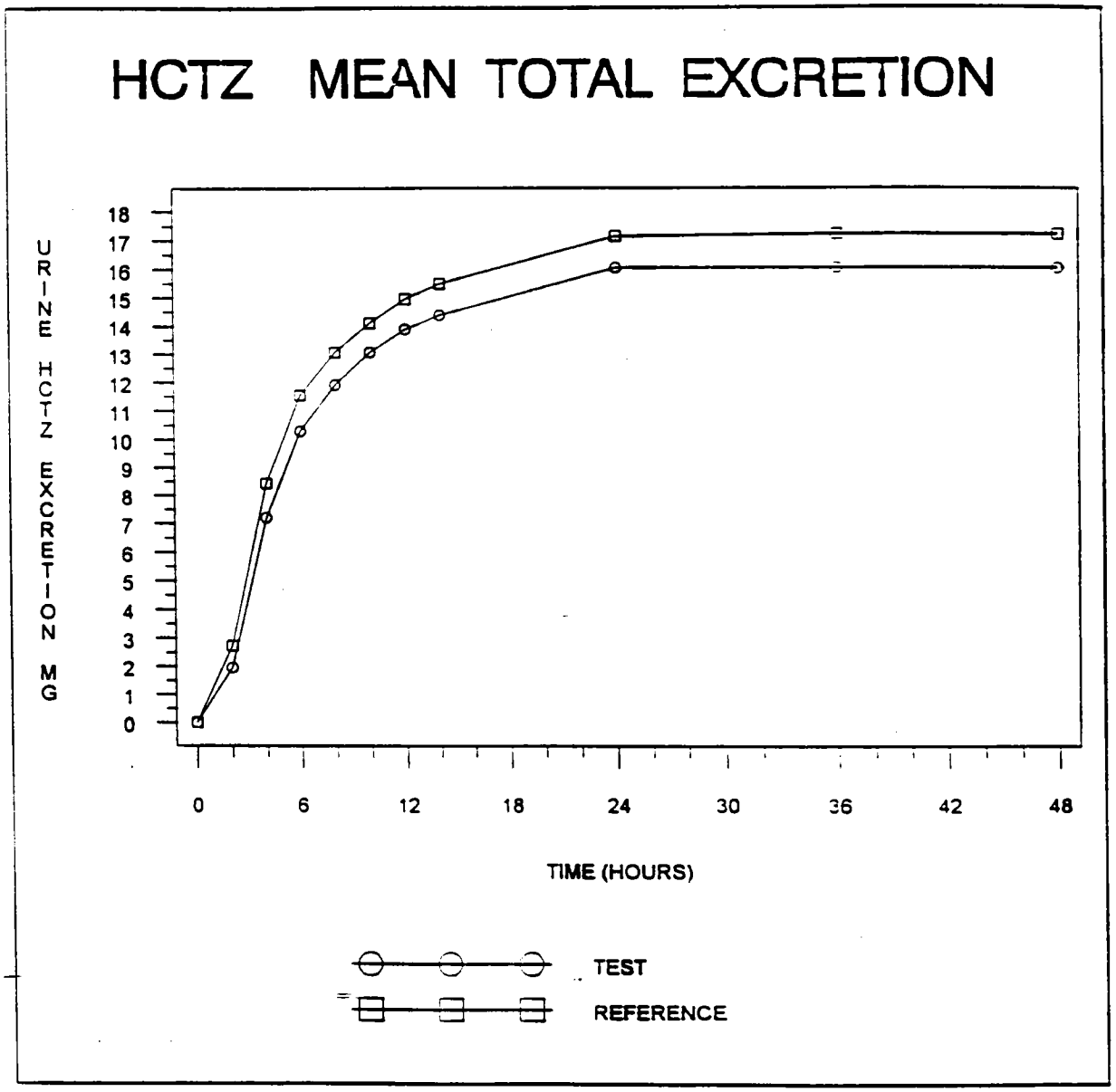

HCTZ MEAN TOTAL EXCRETION
URINE HCTZ EXCRETION MG
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
0
6
12
18
24
30
36
42
48
TIME (HOURS)
TEST
REFERENCE

FIGURE 3A

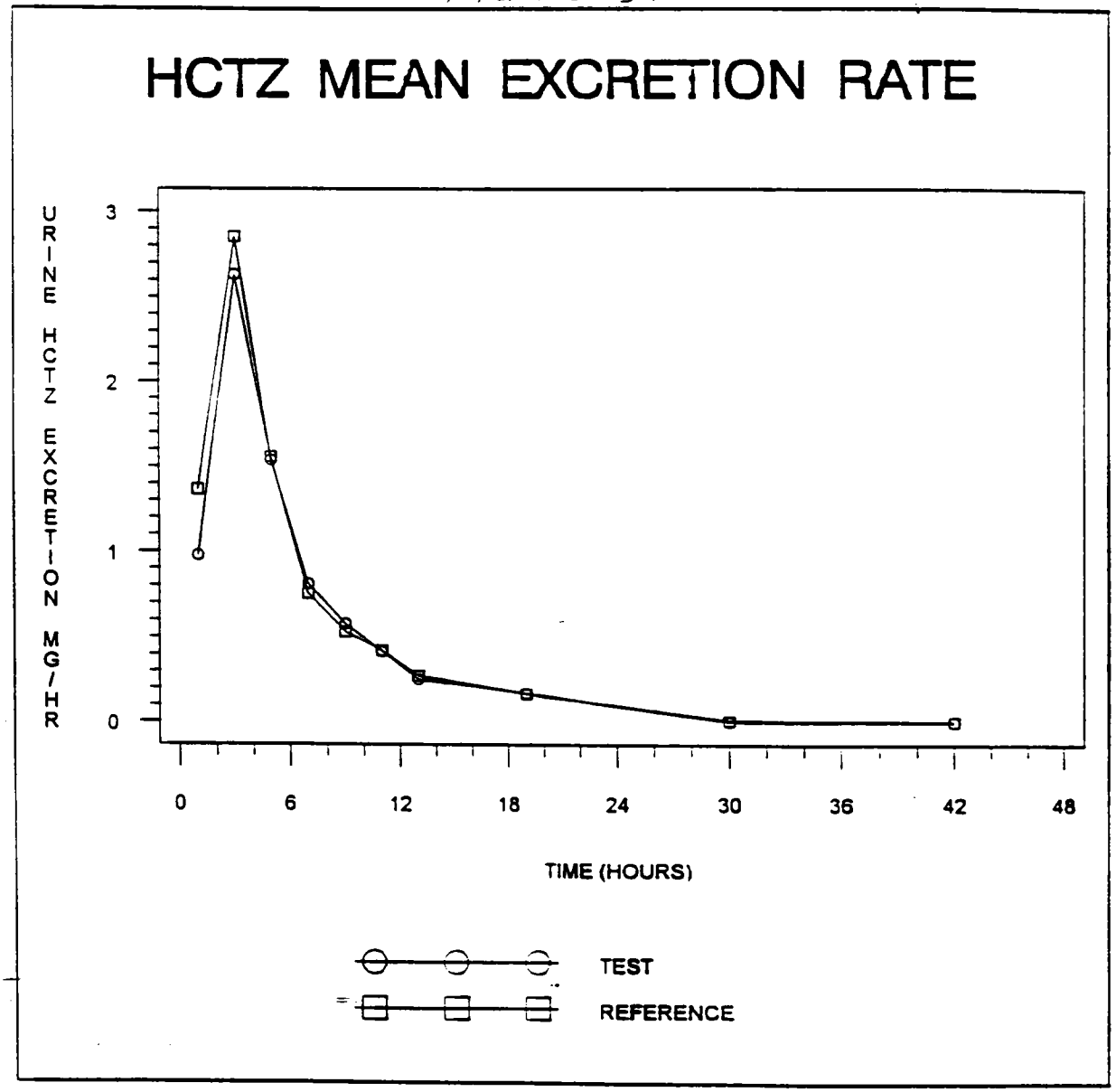

HCTZ MEAN EXCRETION RATE
URINE HCTZ EXCRETION MG/HR
3
2
1
0
0
6
12
18
24
30
36
42
48
TIME (HOURS)
TEST
REFERENCE

FIGURE 4

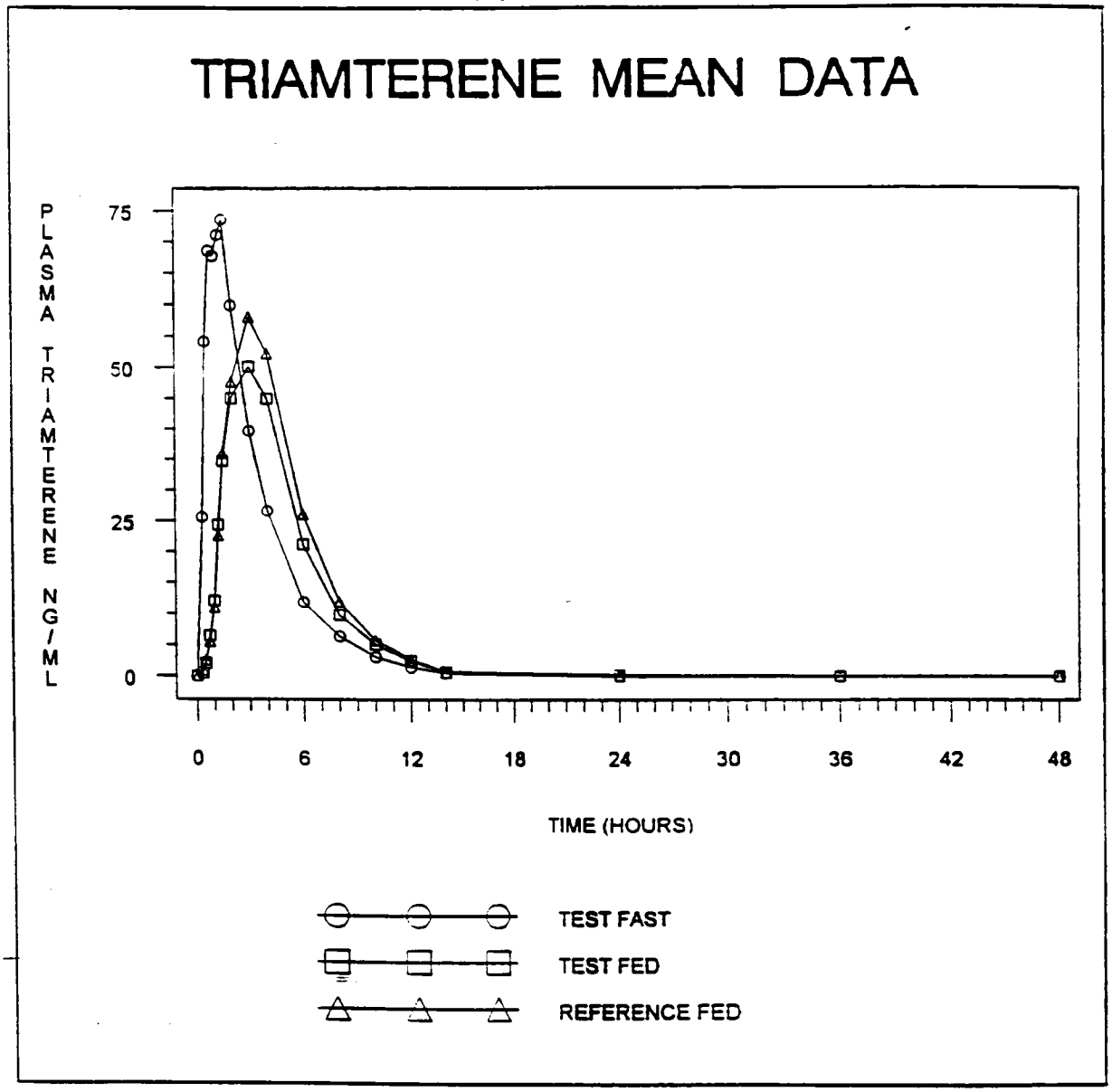

TRIAMTERENE MEAN DATA
PLASMA TRIAMTERENE NG/ML
75
50
25
0
0
6
12
18
24
30
36
42
48
TIME (HOURS)
TEST FAST
TEST FED
REFERENCE FED

FIGURE 5

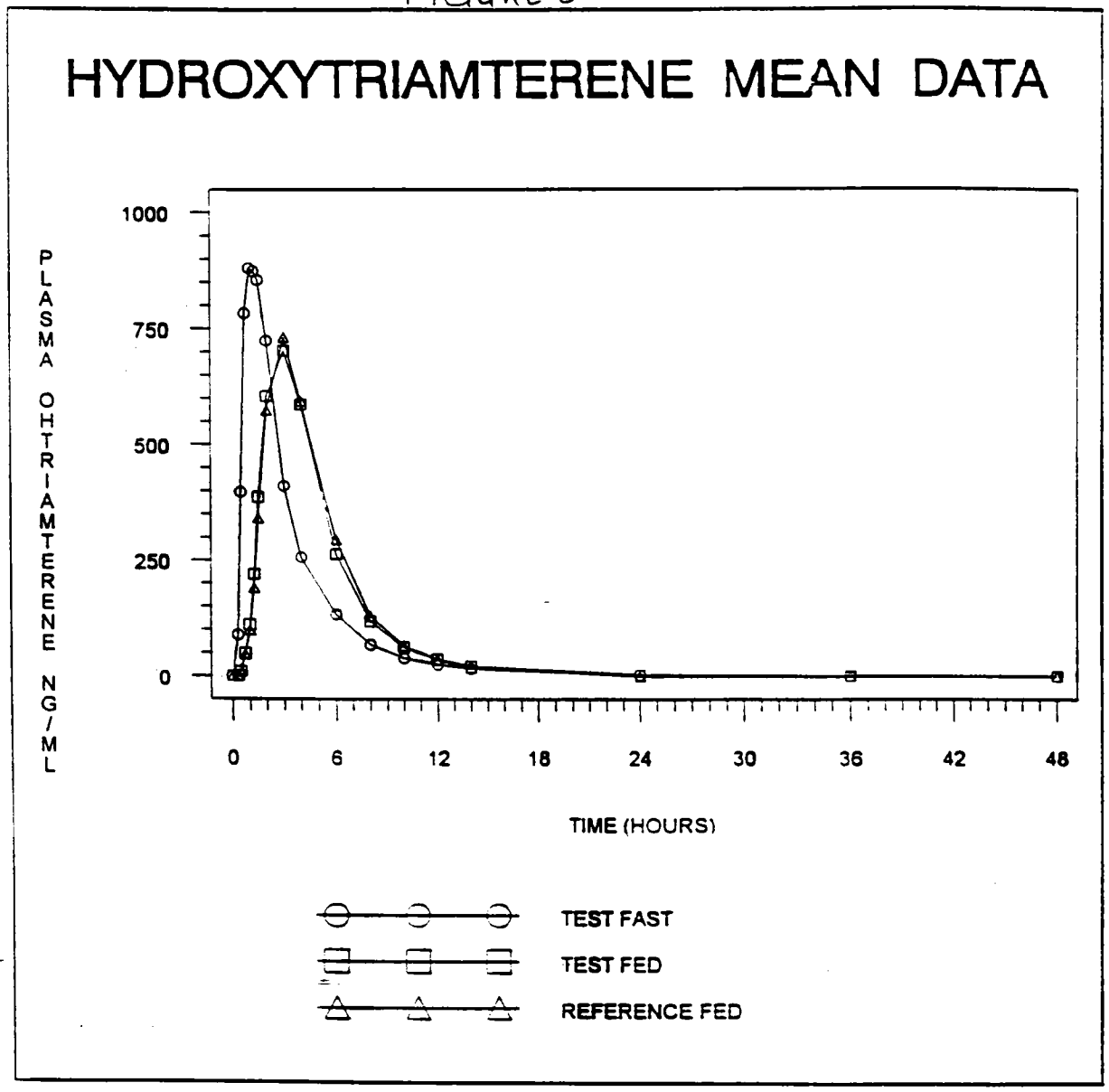

HYDROXYTRIAMTERENE MEAN DATA
PLASMA OHTRIAMTERENE NG/ML
1000
750
500
250
0
0
6
12
18
24
30
36
42
48
TIME (HOURS)
TEST FAST
TEST FED
REFERENCE FED

FIGURE 6

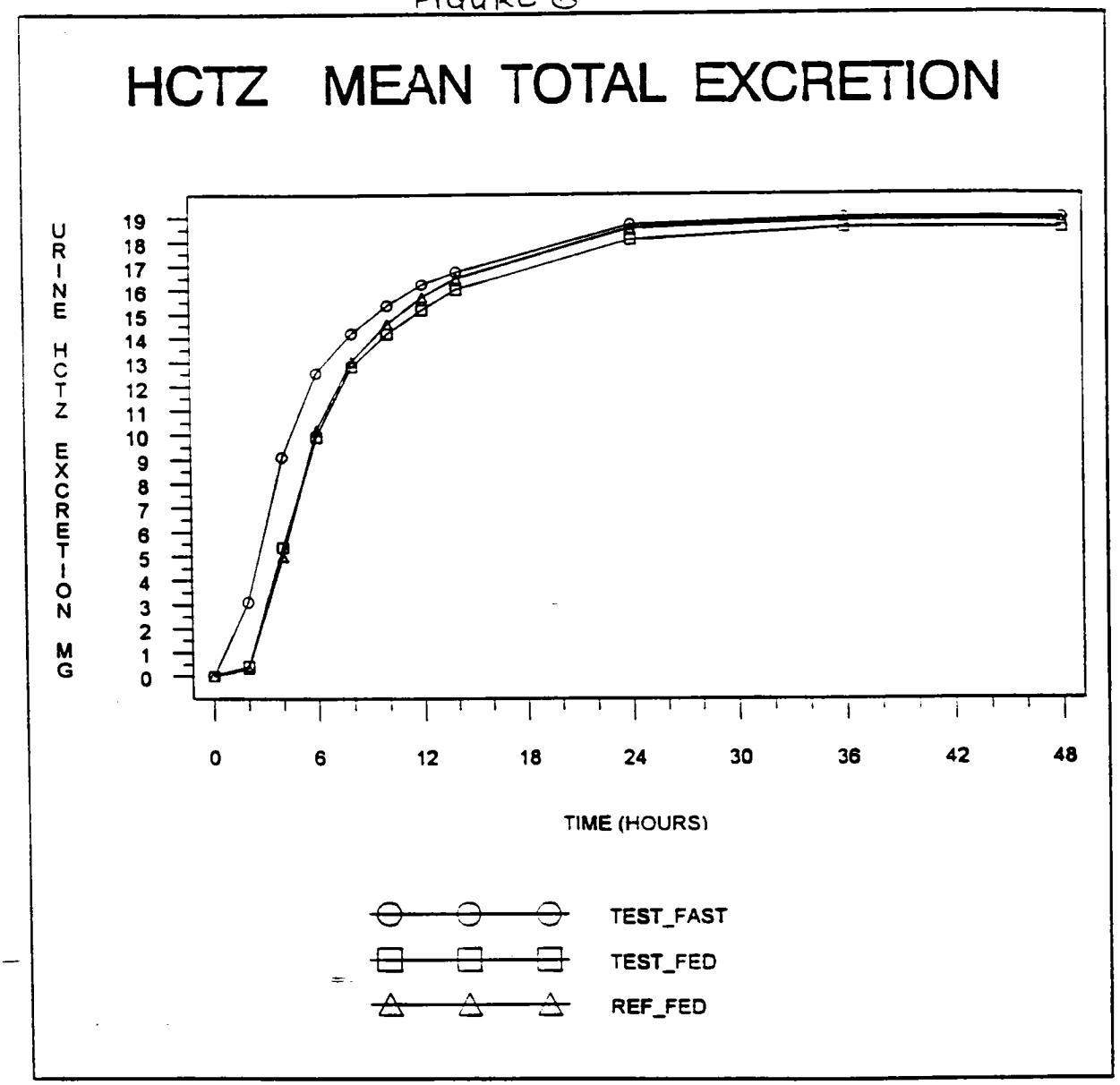
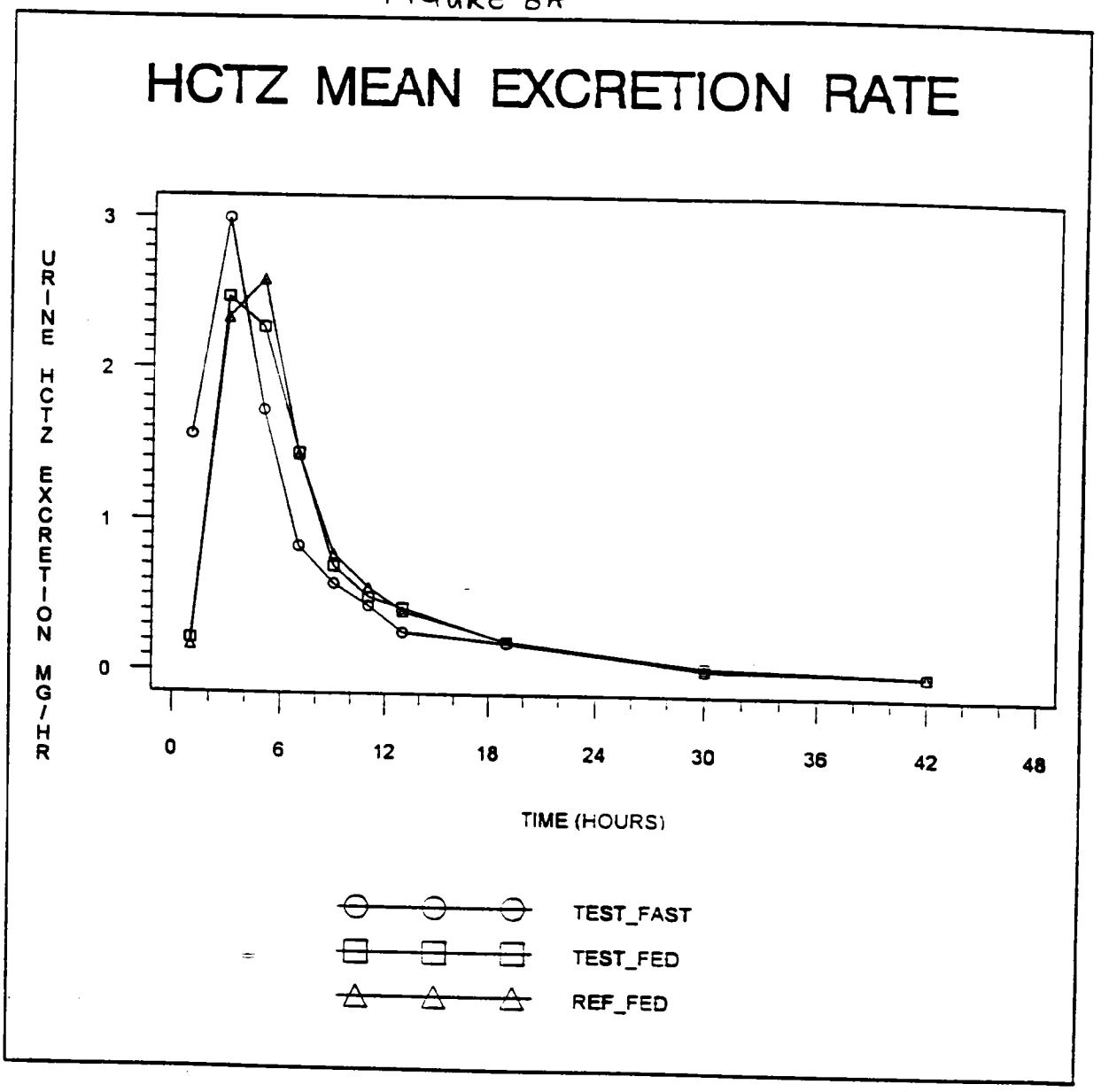

HCTZ MEAN TOTAL EXCRETION
URINE HCTZ EXCRETION MG
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0
6
12
18
24
30
36
42
48
TIME (HOURS)
TEST_FAST
TEST_FED
REF_FED

FIGURE 6A


HCTZ MEAN EXCRETION RATE
URINE HCTZ EXCRETION MG/HR
3
2
1
0
0
6
12
18
24
30
36
42
48
TIME (HOURS)
TEST_FAST
TEST_FED
REF_FED